Managing Progression of Metastatic GIST

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Overview

- Types of progression and clinical impact
- Biology of progression – KIT resistance mutations
- Tools for identifying individual mutation spectrum
- Therapies for localized progression
- Therapies for widespread progression

Patient Case #1

- 62 yo F who presented with abdominal pain and weight loss in 2016. CT imaging revealed multiple liver lesions and peritoneal implants without a clear primary tumor.
- Liver lesion biopsied and showed spindle cells, CD117+, DOG1+. KIT mutation testing revealed an exon 11 mutation.
- Initiated on imatinib 400 mg daily. Scans showed shrinkage and necrosis of the lesions by 6 months of therapy.
- Continued on therapy for 2 years. Presents for a routine scan which shows an enlarging lesion in segment VII of the liver.

Patient Case #1

Progressive GIST lesions:

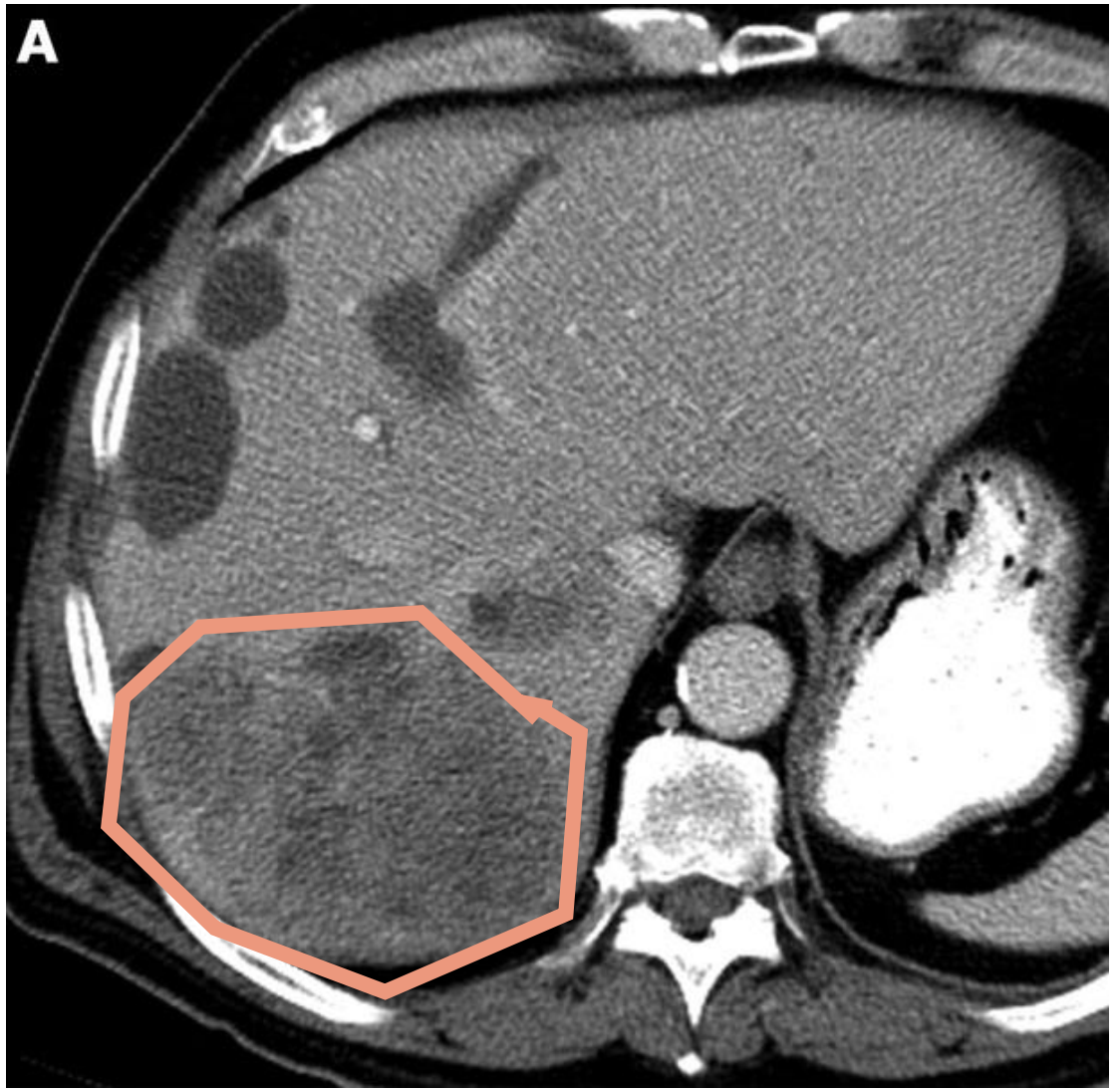
Increased density and enhancement (glow)

PET-avid

Size not always reliable

Stable, necrotic lesions (dead)

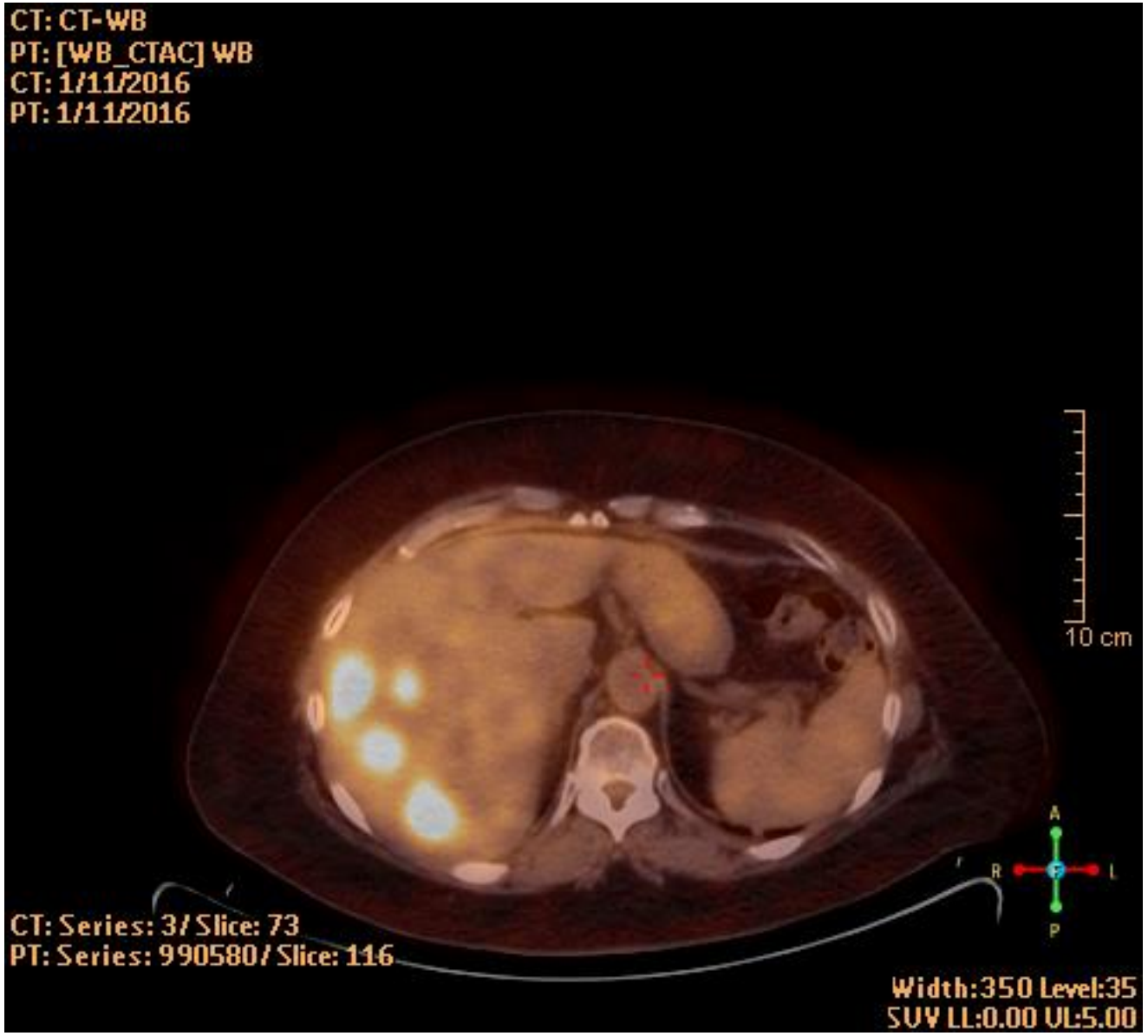
Progressing lesion



Kobayashi K, et al. Am J Clin Oncol. 2009.

Patient Case #2

- 40 yo F who presented with GI bleeding, imaging showed 10 cm duodenal mass and multiple liver lesions.
- Underwent emergent resection of primary lesion, and liver biopsied. Intraoperatively found to have multiple 2 cm omental implants. Pathology showed spindle cells, CD117+, DOG1+. KIT mutation testing revealed an exon 9 mutation.
- Initiated on imatinib 400 mg daily x 1 month, then increased to 800 mg daily. Scans showed stable disease x 6 months, then imaging showed multiple new PET avid lesions in the liver.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PT: [WB_CTAC] WB
CT: 1/11/2016
PT: 1/11/2016
10 cm
A
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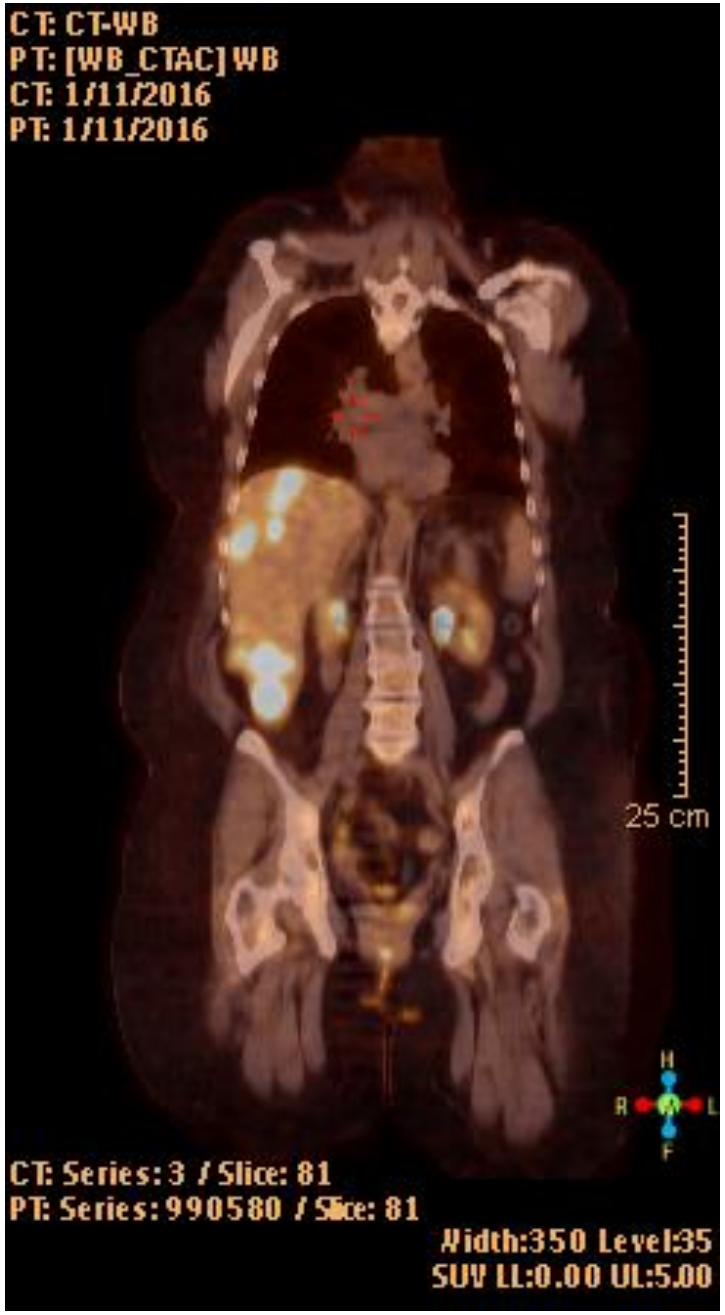
CT: Series: 3/ Slice: 73
PT: Series: 990580/ Slice: 116
Width:350 Level:35
SUV LL:0.00 UL:5.00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PT: [WB_CTAC] WB
CT: 1/11/2016
PT: 1/11/2016
25 cm
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CT: Series: 3 / Slice: 81
PT: Series: 990580 / Slice: 81
Width:350 Level:35
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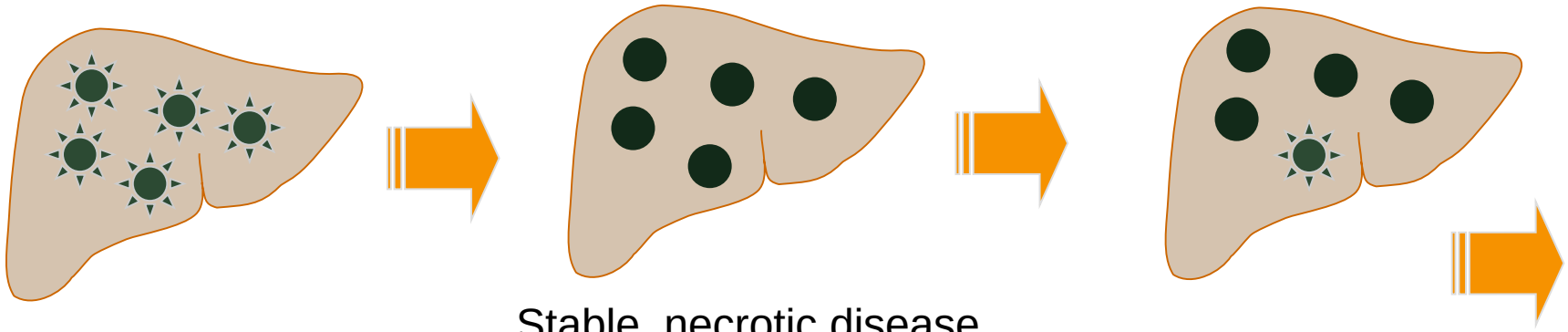
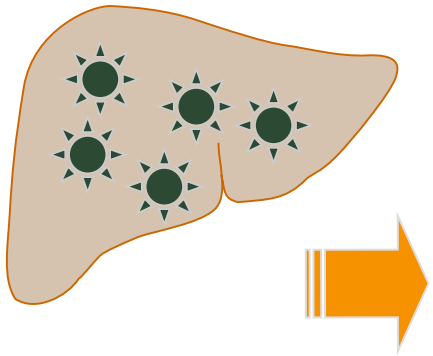
Types of progression: limited or widespread



Stable, necrotic disease

LIMITED PROGRESSION
Address resistant lesion
Keep imatinib on for others

Development of new mutations that lead to imatinib resistance



WIDESPREAD PROGRESSION
Change therapies
Recheck mutation testing

Stable lesion

Progressing lesion

Understanding KIT mutations

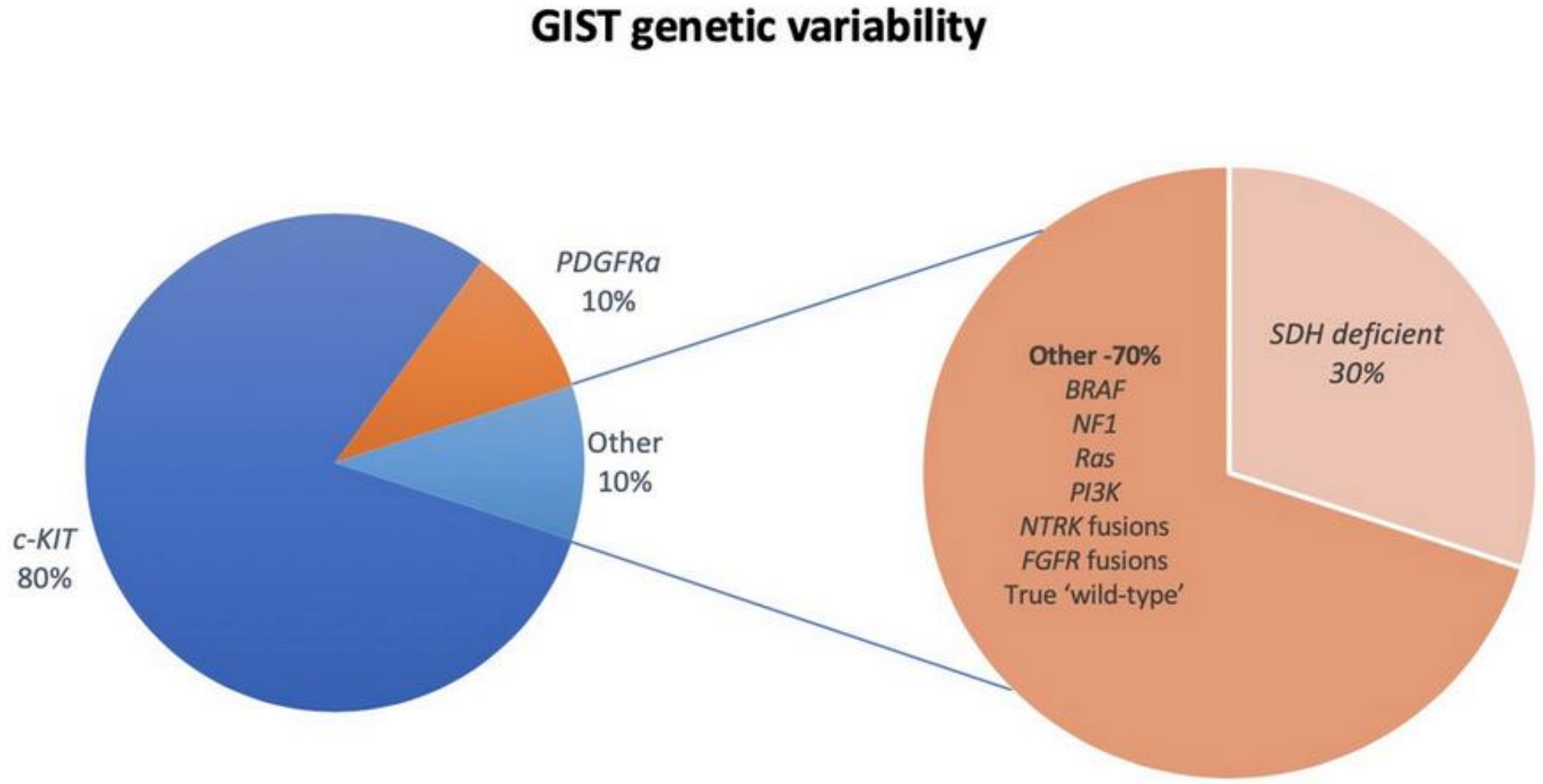
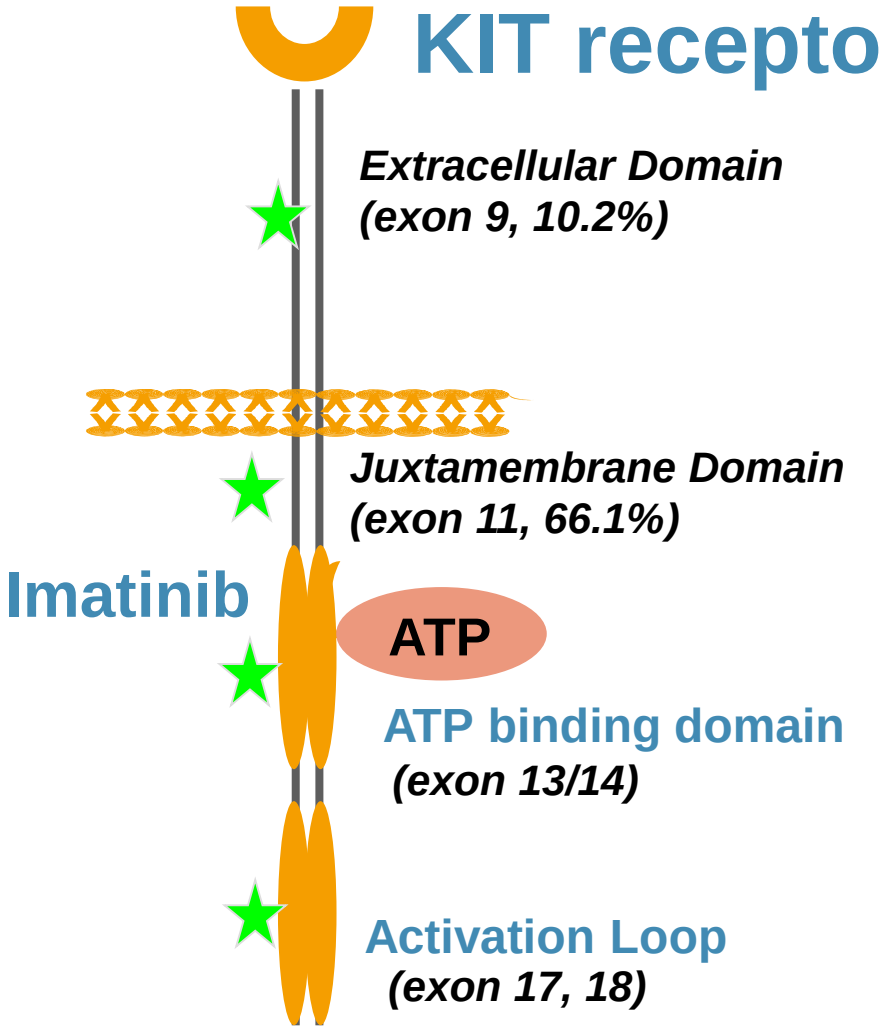


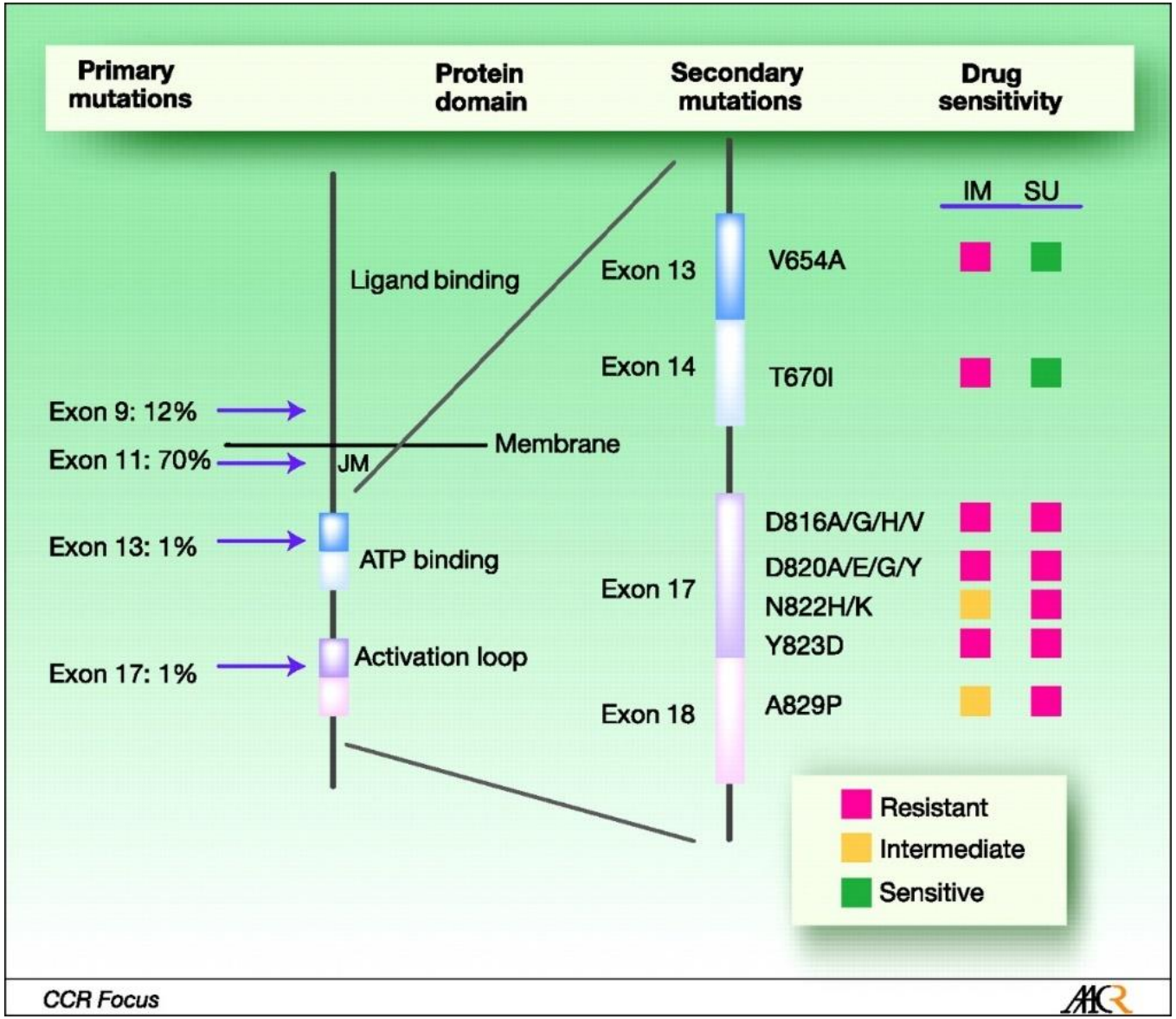
Figure 1. Mutational landscape of GISTs.

Florou et al, Discov Med 2020

Understanding KIT mutations



★ = common mutation site



Gramza et al. Clin Cancer Res 2009

Managing local/nodular progression

- Suggests only one area with resistant clone developing
- Can target the resistant lesion, instead of abandoning the systemic therapy that is controlling most of the disease

TREATMENT OPTIONS

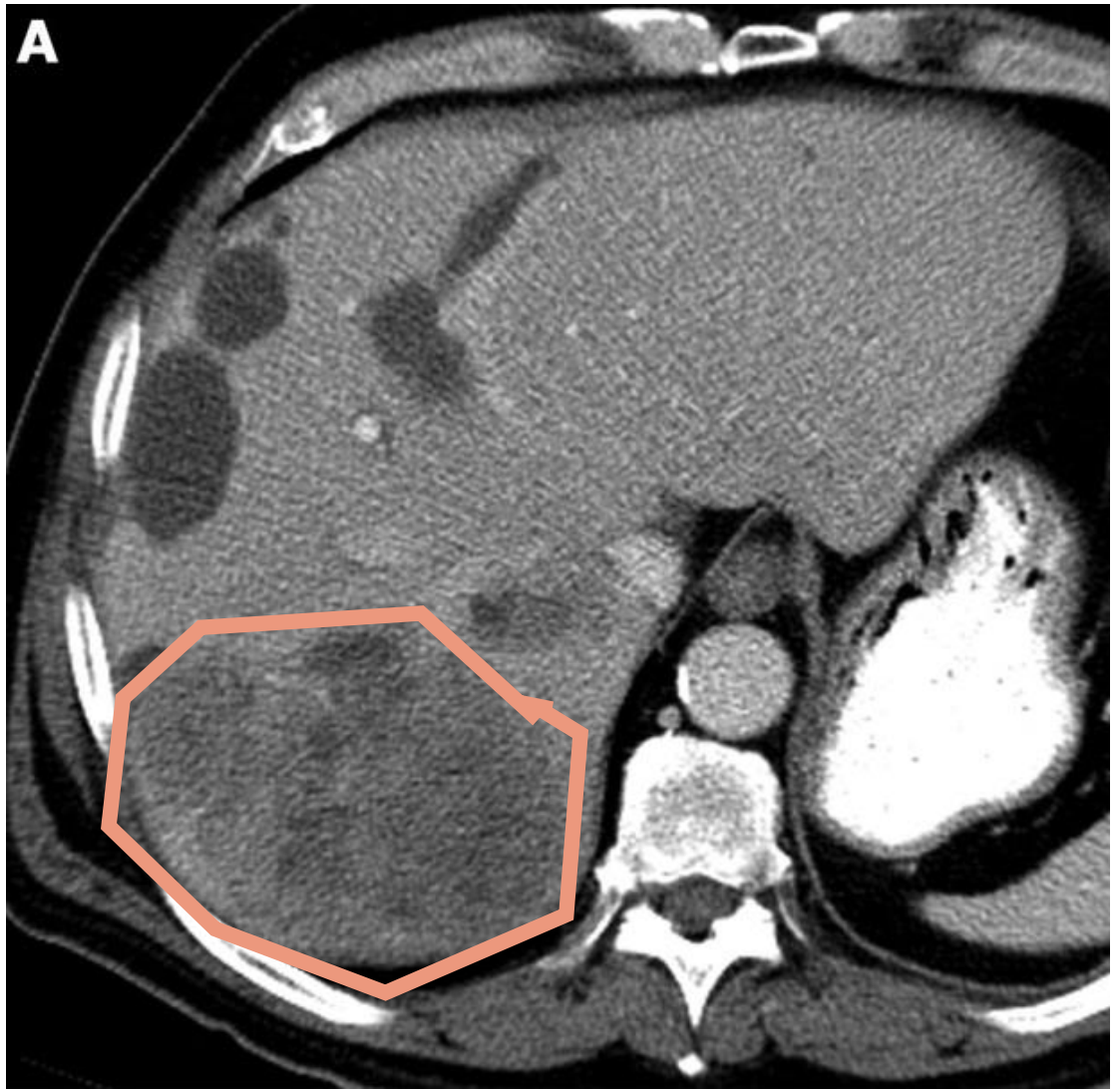
Surgical resection

Stereotactic radiation (SBRT)

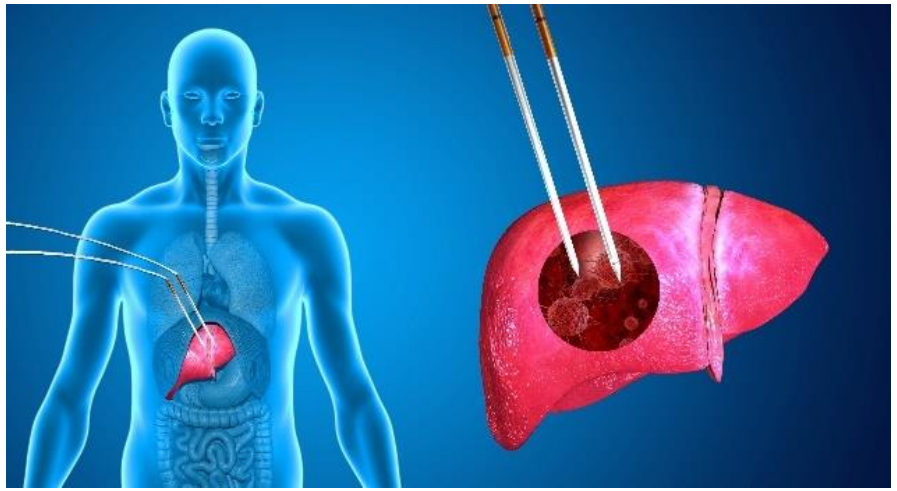
Embolization (bland, radio (Y-90), chemo)

Ablation (cryo, radiofrequency)

Electroporation (Nanoknife)

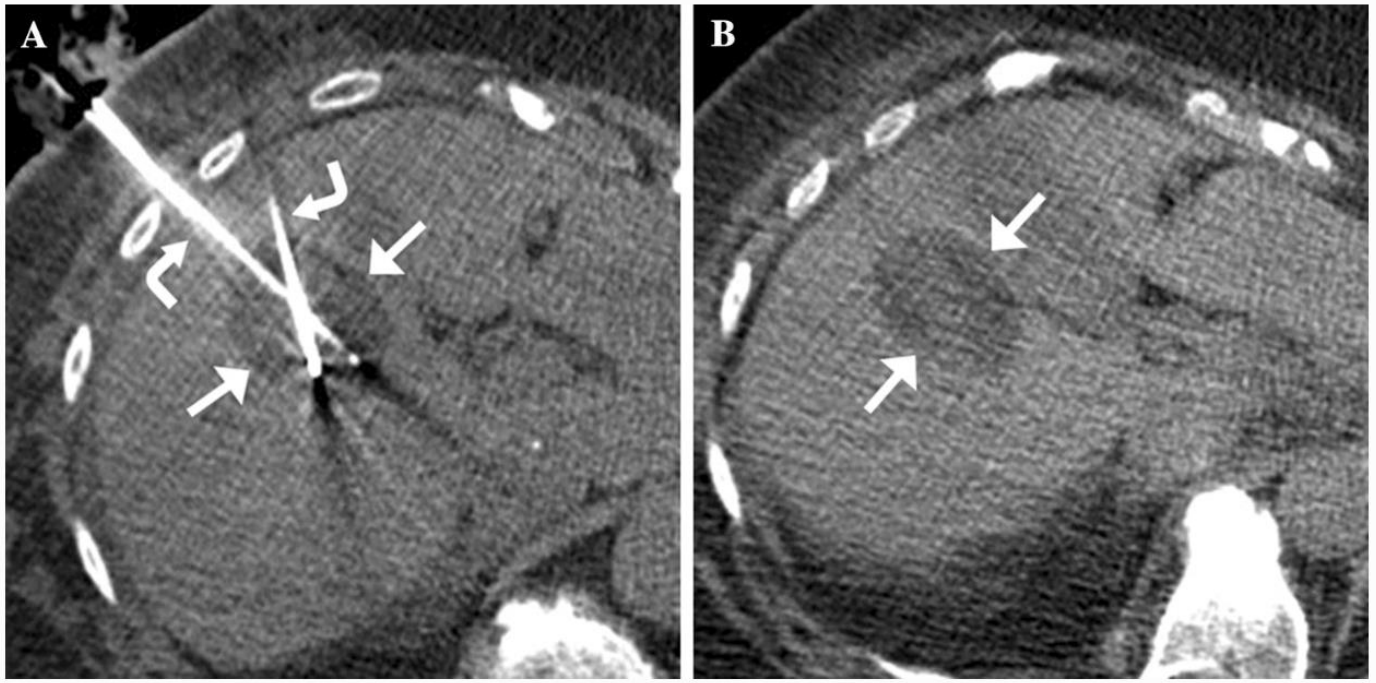


Managing local/nodular progression



Ablation – inserting needles through skin into lesion to transmit heat, cold, microwave, electricity

Embolization – access the blood vessels supplying the tumor lesion to deliver blocking material, chemo, radioparticles

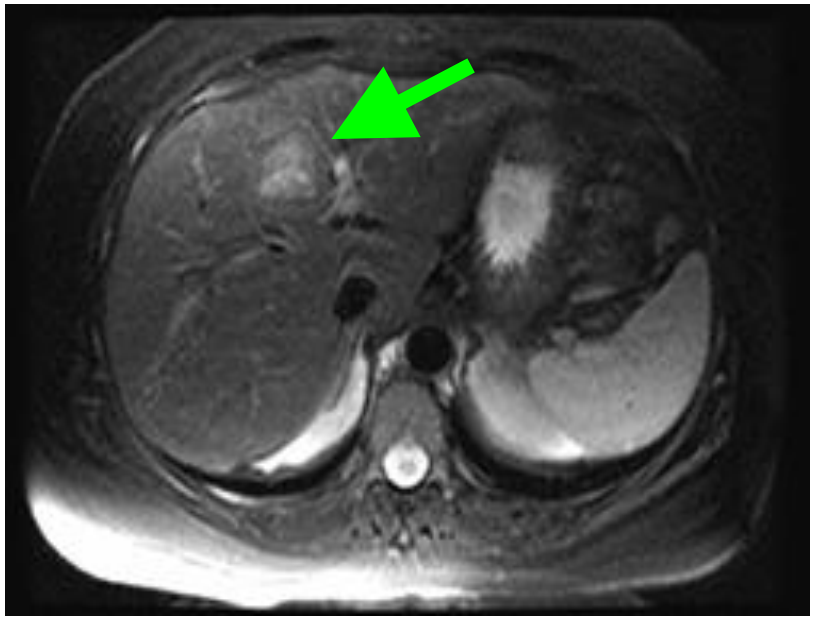


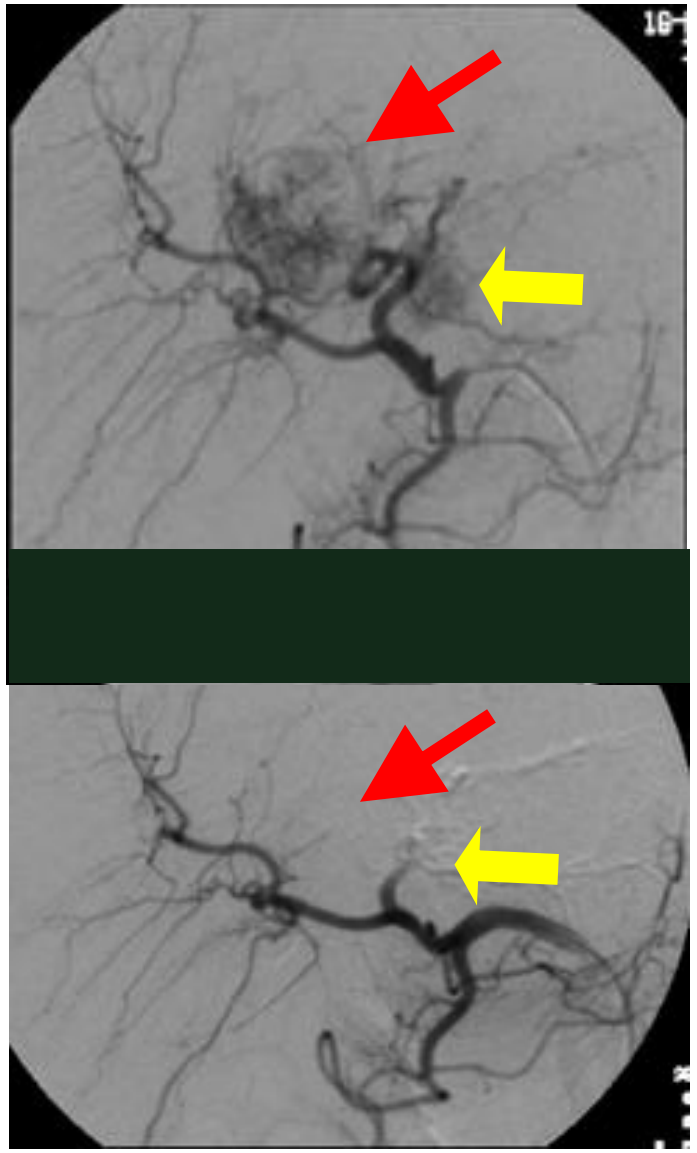
Eighty-two-year-old female who underwent CT-guided cryoablation of a breast cancer metastasis. **a** Axial, intra-procedural, unenhanced CT image obtained during cryoablation reveals two cryoprobes (curved arrows) in the right hepatic lobe within the target mass and surrounded by the sharply-marginated hypoattenuating ice ball (straight arrows). **b** Axial, unenhanced CT image obtained immediately after cryoablation reveals the ovoid hypoattenuating ice ball (arrows) which is just beginning to thaw

Ratanaprasatporn et al Abd Radiol 2019

Hepatic artery embolization

Pre-embolization

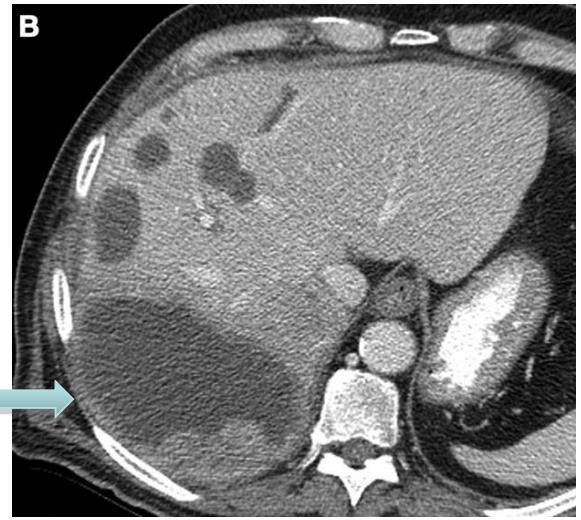




Post-embolization

Stable, Hypoattenuating Lesions

Embolized Lesion



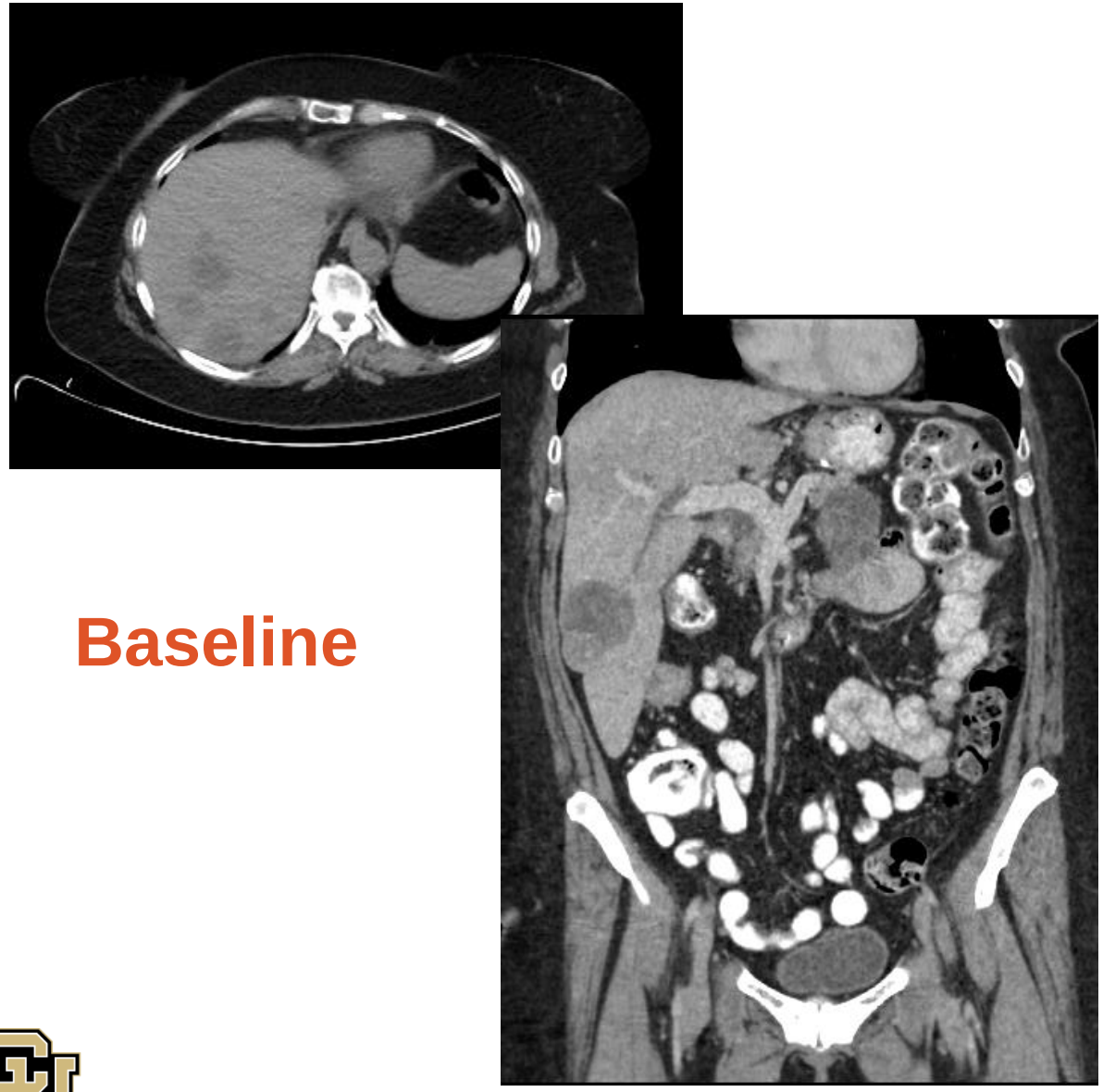
Kobayashi, K, et al. Am J Clin Oncol. 2009;32:574-581. Courtesy of Dr. R. DeMatteo.

Approach to widespread progression

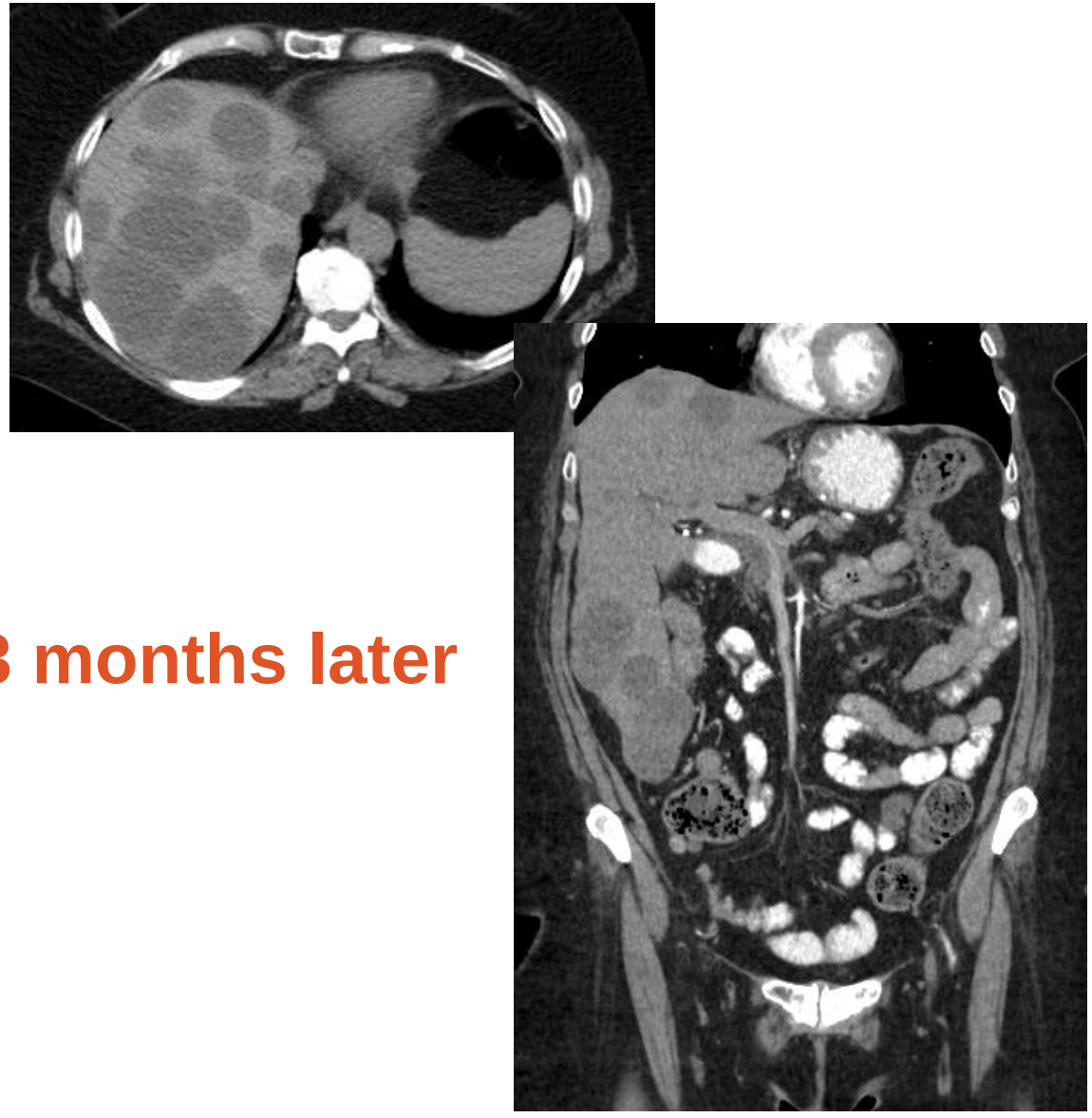
Clinical “pearls”

- Confirm active disease with PET/CT or contrast enhanced CT – beware of pseudoprogression
- Patients who recur after stopping adjuvant imatinib will almost always respond if you restart –don’t assume resistance
- Step one for progression on imatinib 400 mg is to attempt dose escalation to 600 mg or 800 mg
  - Patients may tolerate split dosing better (ie 400 mg twice daily)
- For oligometastatic recurrence/progression, especially first line, consider being aggressive (ie surgery, ablation, etc) once downstaged
- Biopsy progressing, not stable lesions

Pseudoprogression – don’t be fooled!

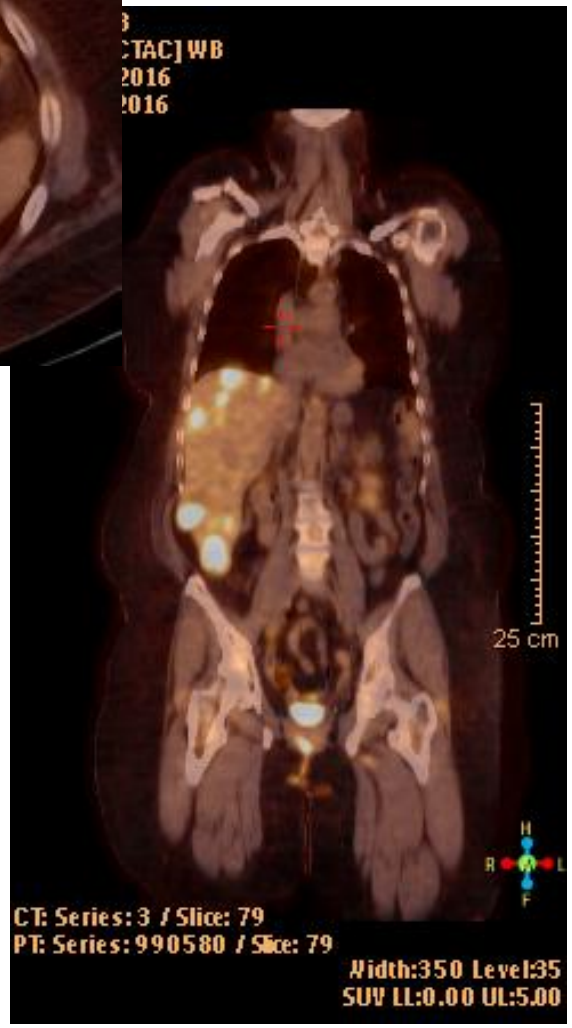


Baseline

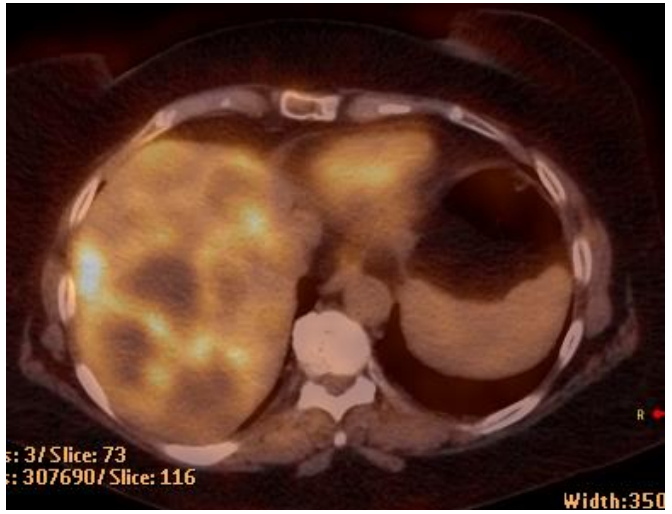


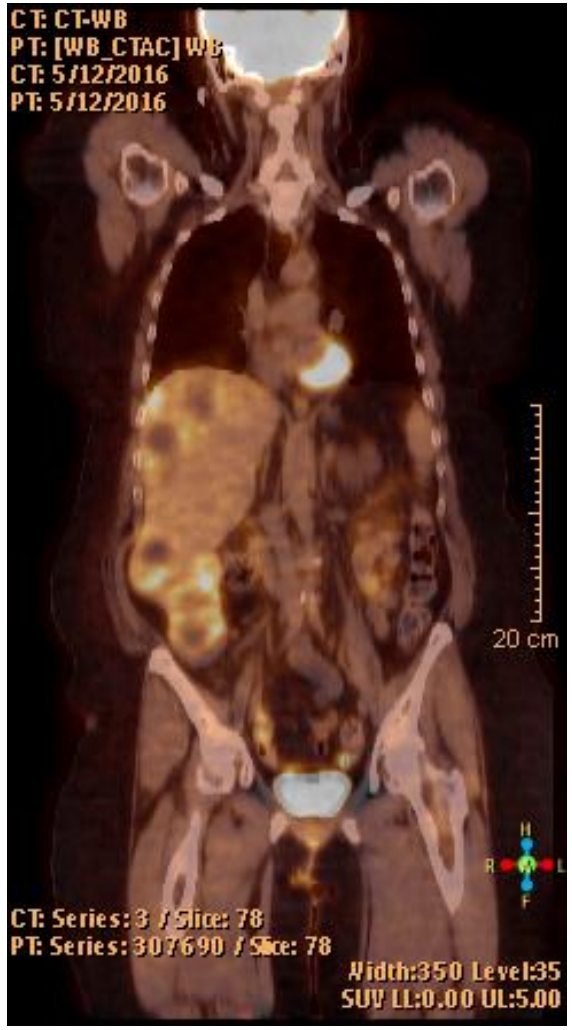
3 months later

Pseudoprogression – don't be fooled!



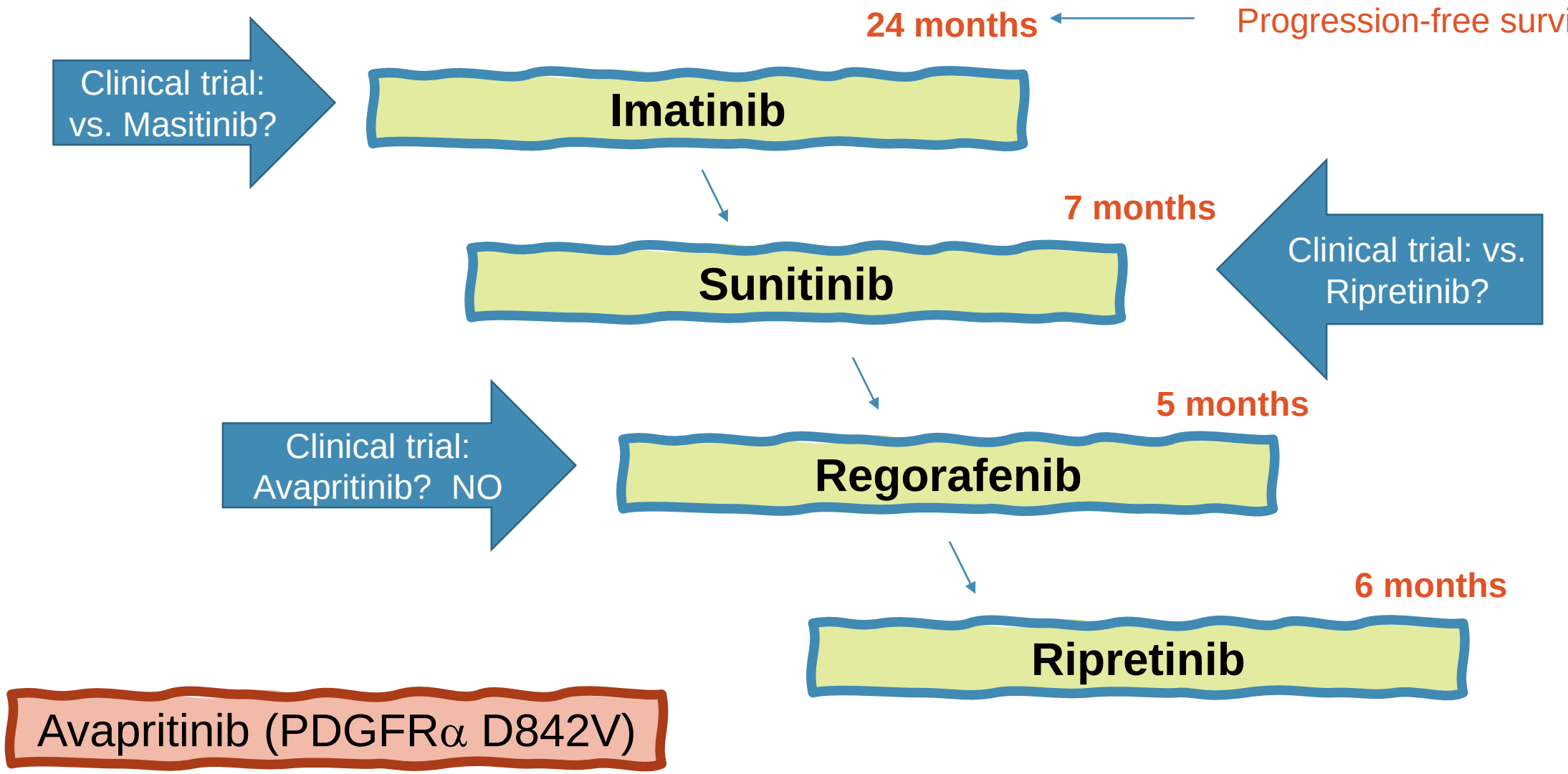
Baseline





3 months later

Approach to unresectable, progressing GIST



5th line or greater

- Dasatinib
- Nilotinib
- Sorafenib
- Cabozantinib
- Avapritinib
- Pexidartinib
- Ponatinib
- Pazopanib

CLINICAL TRIALS! → Immunotherapy?
Other targets and combinations?

Mutation testing for new resistance mutations: can this help guide therapy?

Activity of TKIs against various mutations

Drug	KIT							PDGFRα			
	Primary Mutations			Secondary Mutations							
	Exon 8	Exon 9	Exon 11	Exon 13	Exon 14	Exon 17	Exon 18	Exon 12	Exon 14	Exon 18	Exon 18 D842V
Imatinib											
Sunitinib											
Regorafenib						*					
Avapritinib											
Ripretinib											
Sorafenib											
Cabozantinib											
Dasatinib											
Ponatinib											

Sensitive | Intermed. | Resistant | Insuff data

* Except D816V - resistant

Modified from Table 1, Florou et al, Discov Med 2020

Factors that impact choice of drugs

- **Mutation data**
  - Repeating tumor biopsy? (sampling limitations)
  - ctDNA – lower sensitivity

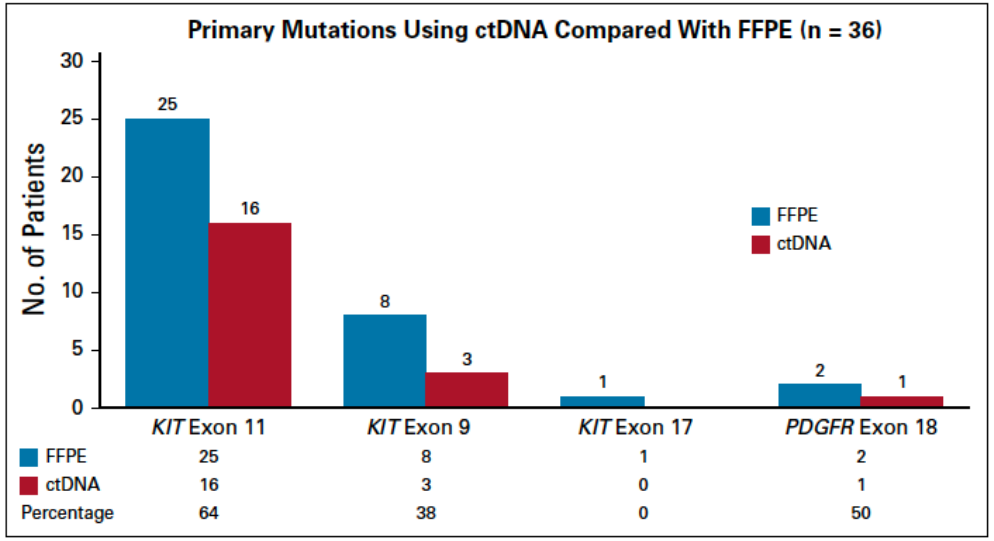


TABLE 1. Utility of ctDNA in the Management of Metastatic and Progressive GI Stromal Tumor

Variable	ctDNA Mutation Positive	Tumor FFPE Mutation Positive	Detection Rate, %
All patients (n = 36)	20	36	56
Primary tumor	0	3	0
Metastatic low burden and responding	0	8	0
Metastatic low burden and progressive	0	5	0
Metastatic high burden and responding	1	1	100
Metastatic high burden and progressive	19	19	100

Abbreviations: ctDNA, circulating tumor DNA; FFPE, formalin-fixed paraffin-embedded.

Arshad et al, JCO Precis Oncol 2020

Factors that impact choice of drugs

- **Side effect profiles**
- Frequent dose reductions required (esp. sunitinib, regorafenib, avapritinib)

	Common	Serious	Interactions
KIT selective • Imatinib 600/800 • **Avapritinib**	Fatigue, arthralgias, nausea/diarrhea	Edema, **cognitive dysfunction**, liver toxicity	Grapefruit juice, iron/calcium, warfarin, statins, alcohol
VEGF/other TKs • Sunitinib • Regorafenib • Cabozantinib • Sorafenib • Pazopanib • Ponatinib • **Ripretinib**	Hypertension, hand-foot syndrome, diarrhea, decreased blood counts, thyroid suppression, skin/hair color changes **Rash, alopecia**	Bleeding, thrombosis, GI perforation, heart failure **Skin cancers**	Acid blockers (PPIs)

Summary and take-homes

- Use imaging to confirm extent of progressive disease
- Local modalities can salvage systemic therapies by eliminating resistant clones
- Mutation testing at initial diagnosis is critical
- Rebiopsy and eventually ctDNA to identify resistance mutations may ultimately guide subsequent therapies for progression – but not there yet
- New drugs custom-designed for resistant GIST are offering hope!

Thank you and Questions!!!

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